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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,844	05/14/2001	Yi Hu	LEX-0176-USA	8344

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	7

DATE MAILED: 12/03/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/854,844	Applicant(s) HU ET AL.	
	Examiner Delia M. Ramirez	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-4 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4 is/are rejected.

7)☒ Claim(s) 1 is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Status of the Application

Claims 1-4 are pending.

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it does not identify the citizenship of Inventor No. 3 Andrew Olson. Correction is required.

Claim Objections

2. Claim 1 is objected to because of the recitation of "nucleotide sequence first disclosed" as it is not clear where and when is the instant nucleotide sequence further disclosed. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either an asserted utility or a well established utility.

Before the utility of a nucleic acid molecule (1) comprising the nucleotide sequence of the polypeptide of SEQ ID NO: 2, (2) at least 24 nucleotides of the sequence set forth in SEQ

ID NO: 1, or (3) a nucleic acid molecule that hybridizes under stringent conditions to the molecule of SEQ ID NO: 1, the utility of the entire recited sequences, SEQ ID NO: 1 and SEQ ID NO: 2 must first be addressed. Applicant asserts that SEQ ID NO: 1 encodes a novel human protease (the polypeptide of SEQ ID NO: 2) with homology to animal proteases, in particular serine proteases (page 2 of the specification). Applicant also asserts that the importance of human proteases relies on the fact that proteases have been associated with, *inter alia*, regulation of development, modulation of cellular processes, fertility, and infectious disease (page 1 of the specification). Furthermore, Applicant states that the nucleic acid molecules of the instant application can be used to isolated similar molecules.

However, based upon Applicant's disclosure, the claimed invention does not meet the utility requirement for the following reasons. First, Applicant indicates neither the function of the protein encoded by SEQ ID NO: 1 nor the function of the polypeptide of SEQ ID NO: 2 in claims 1-3. In addition, neither Applicant's disclosure nor the state of the prior art at the time the invention was made provides guidance as to where the important structural elements of serine proteases such as the catalytic domain, binding domain, and the like are located.

Secondly, Applicant provided no empirical evidence that the polypeptide of SEQ ID NO: 2 or the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 1 are serine proteases. The predicted function of the polypeptide of SEQ ID NO: 2 is solely based upon sequence alignments with prior art sequences. The state of the art suggests that sequence identity alone is insufficient to accurately predict its asserted utility, and that sequence comparison should not be used solely to determine function. Bork (Genome Research, 10:348-400, 2000) clearly teaches the pitfalls associated with comparative sequence analysis for

predicting protein function because of known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect , despite the fact sequencing itself is highly automated and accurate (page 398, column 1). One of the reasons for this inaccuracy is that the quality of data available is still insufficient. This is particularly true for data relating to protein function. Protein function is context dependent, and both molecular and cellular aspects must be considered (page 398, column 2). Most features predicted with an accuracy of greater than 70% are of structural nature and, at best, only indirectly imply certain functionality (see page 399, Table 1 legend). Applicant's amino acid sequence SEQ ID NO: 2 has, at best, 31.4% sequence identity with an epidermis specific serine protease. Applicant's nucleic acid sequence SEQ ID NO: 1 has no more than 14.5% nucleic acid sequence homology to the polynucleotide encoding a serine protease (see attached sequence alignments), which is significantly less than Bork's 70%. Smith et al. (Nature Biotechnology 15:1222-1223, 1997) indicates that there are numerous cases in which proteins of very different functions are homologous (page 1222, third column, last paragraph). Furthermore, Brenner (TIG 15:132-133, 1999) teaches the difficulty of accurately infer function from homology and clearly states that most homologs must have different molecular and cellular functions (column 2, second paragraph, page 132). Examples of pitfalls associated with comparative sequence analysis for predicting protein function in enzymes associated with modification of fatty acids are shown by Broun et al. (Science 282:1315-1317, 1998) and Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995). Broun et al. teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase into a desaturase. Similarly, Van de Loo et al. teaches

that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Thus, given the low sequence identities of Applicant's SEQ ID NO: 1 and SEQ ID NO: 2 with sequences of the prior art and given the limitations and pitfalls of using computational sequence analysis, as taught by Bork, Brenner, Broun et al., Van de Loo et al., and Smith et al., it is apparent that the biological function of the polypeptide encoded by the nucleic acid molecule of SEQ ID NO: 1 cannot be accurately predicted based solely upon sequence similarity with a sequence of the prior art.

In regard to claims drawn to a nucleic acid molecule (1) comprising the nucleotide sequence of the polypeptide of SEQ ID NO: 2, (2) at least 24 nucleotides of the sequence set forth in SEQ ID NO: 1, or (3) a nucleic acid molecule that hybridizes under stringent conditions to the molecule of SEQ ID NO: 1, since the corresponding polypeptides lack utility for the reasons set forth above, a nucleic acid molecule (1) comprising the nucleotide sequence of the polypeptide of SEQ ID NO: 2, (2) at least 24 nucleotides of the sequence set forth in SEQ ID NO: 1, or (3) a nucleic acid molecule that hybridizes under stringent conditions to the molecule of SEQ ID NO: 1 would also lack utility. Applicant should note that no working examples of polypeptides comprising the sequence of SEQ ID NO: 2, nucleic acid molecules comprising SEQ ID NO: 1, or nucleic acids comprising at least 24 nucleotides of SEQ ID NO: 1 are set forth in Applicant's disclosure.

In addition there is also no well-established utility for SEQ ID NO: 1. Nucleic acids don't have a well-established utility for hybridization purposes because the encoded protein does not have utility for the reasons indicated above. Thus, for the reasons set forth, the claimed sequences, recombinant nucleic acid molecules containing these sequences, and nucleic acids

capable of hybridizing to said sequences do not have a real-world use and hence lack utility (see Utility Examination Guidelines published in Federal Register/Volume 66, Number 4/Friday, January 5, 2001/Notices; pages 1092-1099).

4. Claims 1-4 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either an asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In case Applicant overcomes this utility rejection by providing convincing evidence in response to this Office Action, the following rejections will apply:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 1, 2, 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 1 is indefinite in the recitation of "the NHP sequence described in SEQ ID NO: 1" as it is unclear what NHP is. It is suggested that if the term "NHP" is an acronym, the entire compound name be recited followed by the corresponding acronym in parentheses when first mentioned in the claims.

7. Claim 2 is indefinite in the recitation of "hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO: 1" as these terms are unclear absent a statement of the

conditions under which the hybridization reaction is performed. Nucleic acids which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions. It is suggested that Applicants state the experimental hybridization and wash conditions in the claim.

8. Claim 3 is indefinite in the recitation of "an isolated nucleic acid molecule according to Claim 1 wherein said nucleotide sequence is present in cDNA" for the following reasons. cDNA is known in the art as a single-stranded DNA molecule complementary to an RNA molecule, synthesized from it by reverse transcription (Genes IV, page 806, Lewin, Fourth Edition), therefore it is unclear how a nucleic acid molecule can be "present" in another molecule. Claim 3 is not further limiting Claim 1 as written.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is directed to any nucleotide comprising at least 24 contiguous bases of the nucleotide sequence set forth in SEQ ID NO: 1. The specification does not contain any disclosure of the function of all DNA sequences that have at least 24 contiguous bases of the nucleotide sequence set forth in SEQ ID NO: 1. The genus of nucleic acid molecules claimed is a large variable genus with the potentiality of encoding many different proteins. As taught by

Broun et al. (Science 282:1315-1317, 1998), as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase into a desaturase. Therefore, many functionally unrelated nucleic acid molecules are encompassed within the scope of the claim, including partial DNA sequences. The specification only discloses a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Thus, one of skill in the art cannot conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

10. No claim is in condition for allowance.

Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of

a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
November 28, 2001

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